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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,879	07/28/2003	Michael M. Sekar	ABIOS.001A	3875

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EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,879	SEKAR ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/04,12/8/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

I. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. With respect to claim 1, step (d) is unclear in that it is unclear if the step is intended to mean that if the fluorescence anisotropy measurement in the presence of a sample is greater than when there isn't a sample, then presence or amount of analyte is identified, or if the step is intended to mean that the a greater anisotropy measurement indicates the presence or an amount of an analyte. If the former interpretation is intended, it is also unclear how the presence or amount of the analyte would be identified.

3. The term "about" in claims 4, 5, is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In particular, it is unclear whether "about 5 μm" would include microspheres with diameters of 3μm.

4. The remaining claims are indefinite due to their dependence on an indefinite claim.

Claim Rejections - 35 USC § 102

II. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 8, 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Potyrailo et al [Potyrailo et al, Adapting selected nucleic acid ligands to biosensors, 1998, Anal Chem 70:3419-3425].

With respect to claim 1, Potyrailo et al teach an anti-thrombin DNA aptamer (p.3419, col.1) immobilized to a glass surface (p.3420, col.1) and the use of fluorescence anisotropy to detect the bound labeled aptamer probe-analyte binding event using a vertically polarized laser (p.3420, col.2).

6. With respect to claim 8, the aptamers comprise 15-mer single-stranded DNA that bind to the blood-clotting factor thrombin (p.3421, col.2).

7. With respect to claim 16, a vertically polarized laser is used to detect fluorescence anisotropy (p.3420, col.2).

8. Claims 1, 9, 11, 12, 14, 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Gold et al [US 6,544,776] in light of Fang et al [Fang et al, Molecular aptamer for real-time

oncoprotein platelet derived growth factor monitoring by fluorescence anisotropy, 2001, 73, 5752-5757].

With respect to claim 1, Gold et al teach aptamers immobilized to the surface of biochips (column 10, lines 60-67), and measurement of fluorescence anisotropy to determine presence of target molecules (column 16, lines 15-36).

Although Gold et al, do not teach illuminating the aptamer with polarized light to measure the amount of fluorescence anisotropy, a person of ordinary skill in the art would know that the use of polarized light is needed, as shown by Fang et al who defines anisotropy (p.5753, col.2).

9. With respect to claim 9, Gold et al teach the use of fluorescein (column 12, lines 16-20).

10. With respect to claims 11-12, Gold et al teach a 4x4 array of aptamers (fig. 1, column 3, lines 28-38).

11. With respect to claim 14, Gold et al teach an array of photoreactive aptamers, where irradiation will covalently attach only the correct protein to the correct photoactivitable aptamer present at a defined area of a matrix laid out on the surface of the chip (column 18, lines 14-20).

12. With respect to claims 17, 18, 21, Gold et al teach that the attached nucleic acid ligands will bind to components of the blood plasma or other bodily fluid of an individual known to be suffering from a particular disease where the target molecules are not found in the bodily fluid of healthy individuals (col. 2, line 65 – col. 3, line 11).

13. With respect to claims 19-20, Gold et al teach that the target molecule can be a protein or metabolite (column 4, lines 45-58).

14. Claims 1, 8, 9, 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Hesselberth et al [Hesselberth et al, In vivo selection of nucleic acids for diagnostic applications, 2000, Rev Mol Biotech, 74, 15-25] in light of Fang et al [Fang et al, Molecular aptamer for real-time oncoprotein platelet derived growth factor monitoring by fluorescence anisotropy, 2001, 73, 5752-5757].

Hesselberth et al teach signaling aptamers comprising 25-mers geared toward isolating individuals with particular attributes from the random sequence population (p.16, col.1), where the aptamers are synthetically labeled with fluorescein (p.19, col.2) and then immobilized on a glass surface. The apatmers can be arranged in discrete sectors of arrays (p.24, col.2). Hesselberth et al further teach that the sensor system can detect ligand-dependant changes in fluorescence anisotropy instead of intensity (p.19, col.2). The change in anisotropy would be dependent on the formation of the protein-ligand complex (p.19, col.2).

Although Hesselberth et al do not teach illuminating the aptamer with polarized light to measure the amount of fluorescence anisotropy, a person of ordinary skill in the art would know that the use of polarized light is needed, as shown by Fang et al who defines anisotropy (p.5753, col.2).

15. With respect to claim 8, the aptamer comprise 25-mers (p.16, col.1).

16. With respect to claim 9, the aptamer is labeled with fluorescein(p.19, col.2).

17. With respect to claims 11-13, different apatmers can be arranged in discrete sectors of arrays, so that the presence and quantities of individual analytes can then be determined (p.24, col.2).

18. With respect to claims 14-15, Hesselberth teach that by varying the ratio of fluoresceinated to non-fluoresceinated nucleotides during transcription should result in populations of aptamers that carry varying numbers of fluorescent reporters, randomly distributed about the sequence and structure of the aptamer (p.19, col.1). Some of the fluorescently labeled aptamers would therefore show increased fluorescence in the presence of a cognate ligand, some would show a decrease, and many would be neutral or inactive (p.19, col.1).

Claim Rejections - 35 USC § 103

III. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-7, 9, 11-13, 16, 19, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al [Lee et al, A fiber-optic microarray biosensor using aptamers as receptors, 2000, Anal Biochem, 282:142-146] in view of Potyrailo et al [Potyrailo et al, Adapting selected nucleic acid ligands to biosensors, 1998, Anal Chem 70:3419-3425].

With respect to claim 1, Lee et al a method of measuring thrombin using antithrombind DNA aptamers immobilized on the surface of silica beads (p. 143, col. 1) and making fluorescent measurements. Lee et al do not teach illuminating the aptamers with polarized light, measuring the fluorescence anisotropy of the fluorophore.

Potyrailo et al, however, teach that the measurement of fluorescent anisotropy with a spectrofluorometer (p. 3420, col. 1), after illumination with polarized light (p.3420, col.2). Fluorescence intensities were determined for select positions of the excitation and emission polarizers (p. 3420, col.2). Potyrailo et al further teach that fluorescence anisotropy effectively discriminates between different surface bound targets and is insensitive to variations in the refractive index of the sample solution (p.3421, col.1).

Therefore it would have been obvious to measure the fluorescence anisotropy, in order to effectively discriminate between different surface bound targets, and to provide insensitivity to variations in the refractive index of the sample solution.

20. With respect to claims 2-3, the beads taught by Lee et al are silica (p. 143, col.1).

21. With respect to claims 4-5, the beads taught by Lee et al have a diameter of 3.1μm (p.143, col.1).

Furthermore, although Lee et al do not teach beads with a diameters of 5μm, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranged involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

22. With respect to claim 6, Lee et al teach that F-thrombin was diluted with PBS, and 10μL of each concentration was brought to the fiber's distal end (where the beads are located) and incubated from 8 min (p.143, col.2).

23. With respect to claims 7, 11, the beads with attached aptamers taught by Lee et al are arranged on microwell arrays (p. 143, col.2).

24. With respect to claim 8, Potyrailo et al teach that the aptamers are 15-mer single stranded DNA that bind to thrombin (p.3421, col.2).

25. With respect to claim 9, the aptamers taught by Lee et al are labeled with fluorescein phosphoramidite (pl 143, col.1).

26. With respect to claims 11, 12, the biosensor array taught by Lee et al contains multiple microwell containing the beads (p. 143, col.2).

27. With respect to claim 13, each addressable location of the biosensor taught by Lee comprises thrombin aptamer beads (p. 144, col.2).

28. With respect to claim 16, Potyrailo et al teach a vertically polarized laser is used to detect fluorescence anisotropy (p.3420, col.2).

29. With respect to claim 19, Lee et al teach that the biosensor is used to measure thrombin (abstract).

30. Claims 1-9, 11-13, 17-19, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al [Lee et al, A fiber-optic microarray biosensor using aptamers as receptors, 2000, Anal Biochem, 282:142-146] in view of Fang et al [Fang et al, Molecular aptamer for real-time oncoprotein platelet derived growth factor monitoring by fluorescence anisotropy, 2001, 73, 5752-5757].

With respect to claim 1, Lee et al a method of measuring an analyte using DNA aptamers immobilized on the surface of silica beads (p. 143, col. 1) and making fluorescent measurements. Lee et al do not teach illuminating the aptamers with polarized light, measuring the fluorescence anisotropy of the fluorophore.

Fang et al, however, teach the detection of oncoprotein PDGF, a potential protein marker for cancer diagnosis (p.5753, col.1) using fluorescence anisotropy, where fluorescence measurements were performed on a spectrofluorometer after illumination with polarized light

(p.5753, col.2). Fang et al further teach that the detection of PDGF using fluorescence anisotropy is expected to be sensitive, convenient, and selective (p.5753, col.2), and is quick and can detect PDGF down to 0.22 nM (p.5757, col.1).

Therefore it would have been obvious in the method of Lee et al to measure fluorescence anisotropy, as suggested by Fang et al, in order to provide an assay for onco-protein and disease related protein detection that is quick, sensitive, convenient, and selective.

31. With respect to claims 2-3, the beads taught by Lee et al are silica (p. 143, col.1).

32. With respect to claims 4-5, the beads taught by Lee et al have a diameter of 3.1μm (p.143, col.1).

Furthermore, although Lee et al do not teach beads with a diameters of 5μm, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranged involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

33. With respect to claim 6, Lee et al teach that F-thrombin was diluted with PBS, and 10μL of each concentration was brought to the fiber's distal end (where the beads are located) and incubated from 8 min (p.143, col.2).

34. With respect to claims 7, 11, the beads with attached aptamers taught by Lee et al are arranged on microwell arrays (p. 143, col.2).

35. With respect to claim 8, Lee et al teach that the aptamers are 15-mer single stranded DNA that bind to thrombin (p.143, col.1).

36. With respect to claim 9, the aptamers used by Lee et al are labeled with fluorescein phosphoramidite (pl 143, col.1).

37. With respect to claim 12, the biosensor array taught by Lee et al contains multiple microwells containing the beads (p. 143, col.2).

38. With respect to claim 13, each addressable location of the biosensor taught by Lee et al comprises thrombin aptamer beads (p. 144, col.2).

39. With respect to claim 17-19, 21, Fang et al teach the detection of oncoprotein PDGF, a potential protein marker, for developing an assay for cancer diagnosis (p.5753, col.1).

40. Claims 17-19, 21 rejected under 35 U.S.C. 103(a) as being unpatentable over Potyrailo et al [Potyrailo et al, Adapting selected nucleic acid ligands to biosensors, 1998, Anal Chem 70:3419-3425] in view of Fang et al [Fang et al, Molecular aptamer for real-time oncoprotein platelet derived growth factor monitoring by fluorescence anisotropy, 2001, 73, 5752-5757].

With respect to claims 17-19, 21, Potyrailo et al teach a method for detecting an analyte in a sample. Potyrailo et al do not teach that the detection of an analyte that is associated with a disease or disorder, or that the sample is obtained from a patient suspected of suffering from a disease or disorder.

Fang et al, however, teach the detection of oncoprotein PDGF, a potential protein marker for cancer diagnosis (p.5753, col.1). Fang et al further teach that the detection of PDGF using fluorescence anisotropy is expected to be sensitive, convenient, and selective (p.5753, col.2), and is quick and can detect PDGF down to 0.22 nM (p.5757, col.1).

Therefore it would have been obvious in the method of Potyrailo et al to detect PDGF, as suggested by Fang et al, in order to provide an assay for onco-protein and disease related protein detection that is quick, sensitive, convenient, and selective.

41. Claims 1-6, 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lakowicz et al [Lakowicz et al, Anisotropy-based sensing with reference fluorophores, 1998, Anal Biochem, 267, 397-405] in view of Spiridonova et al [Spridonova et al, DNA aptamers as radically new recognition elements for biosensors, June 2002, Biochem, 67, 706-709].

With respect to claim 1, Lakowicz et al teach measurements of steady-state anisotropies in the presence of reference flurophores with known anisotropies using a protein binding sensor, providing a weighted average of the anisotropies of the emitting spiecies (p.397, cols. 1-2). An air-cooled argon ion laser was used for excitation (p.398, col.2) and the laser excitation was vertically polarized (p.399, col.1). Lakowicz et al, however, do not specify the sensors are fluorophore-labeled aptamers bound to a solid support.

Spiridonova et al, however, teach the use of porous silica microspheres with immobilized DNA aptamers (p.707, col.2), and further teach that DNA aptamers have a very highly ordered tertiary structure, which allows them to form stable and specific complexes with different targets (p.706, col.2), and that the use of porous silica microspheres with immobilized DNA aptamers demonstrates new possibilities for multi-analyte detection, and can be reused many times without loss of sensitivity (p. 708, col. 2).

Therefore it would have been obvious to use porous silica microspheres with immobilized DNA aptamers, as suggested by Spiridonova et al, as the protein binding sensor in the method of Lakowicz, in order to form stable and specific complexes with different targets, and to allow the sensor to be reused many times without a loss of sensitivity.

42. With respect to claims 2-5, Spiridonova et al teach porous silica microspheres with a diameter of 3 μm.

43. Should the limitation in claim 5 that the beads have diameters of about 5 μm not include microspheres with diameters of 3 μm, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranged involves only routine skill in the art. *In re Aller*, 105 USPQ 233. Therefore it would have been obvious for a person of ordinary skill in the art to use microspheres with diamters of about 5 μm through normal optimization techniques.

44. With respect to claim 6, the microspheres of Spiridonova et al are placed into microwells and a solution is pipetted onto the microwells (p.707, col.2).

45. With respect to claim 8, Spiridonova et al teach that the aptamers comprise 15-mers (p. 707, col.2).

46. With respect to claims 9-10, Lakowicz et al teach the use of 6-carboxyfluoroscein (p.397, col.2).

Conclusion

47. No claims are allowed.

48. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

49. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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